ABSTRACTS

24th American Heart Association International Conference on Stroke and Cerebral Circulation

February 4–6, 1999
Opryland Hotel
Nashville, Tennessee

Cosponsoring Organizations:

Joint Section of Cerebrovascular Surgery of The American Association of Neurological Surgeons

Heart and Stroke Foundation of Canada

The Society for Vascular Surgery

The American Neurological Association

The American Heart Association is accredited by the Accreditation Council for C ntinuing Medical Education to sponsor continuing medical education activities for physicians.

The American Heart Association will designate this continuing medical education activity for credit on an hour-per hour basis in Category I of the Physician's Recognition Award of the American Medical Association. Exact number of hours to be determined.

Application for credit has been made to the American Association of Neuroscience Nurses.

Application for credit has been made to the Joint Committee on Education of the American Association of Neurological Surgeons and the Congress of Neurological Surgeons.

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Applicants: David J. Pinsky
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Exhibit 24

2:40 **Preliminary Safety Report of an Ongoing Dose-Escalation Trial of Abelximab in Acute Ischemic Stroke** 74
Harold Adams, University of Iowa, Iowa City, IA

2:50 **The Greater Cincinnati t-PA Experience After the NINDS Trial: Does a Longer Time to Treatment Within the Current Three-Hour Window Reduce Efficacy?** 75
Daniel S. Kanter, Rashmi Kothari, Arthur Pancioli, Edward Jauch, Thomas Brott, James Gebel, Judith Spilker, Tiepu Liu, Joseph Broderick, University of Cincinnati, Cincinnati, OH

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John R. Marler, Barbara C. Tilley, Mei Lu, Thomas Brott, Patrick Lyden, Joseph P. Broderick, James Grotta, Steven R. Levine, Michael Frankel, Stephen Horowitz, Thomas Kwiatkowski, The NINDS rt-PA Stroke Study Group, Long Island Jewish Hospital, NY, Emory University, Atlanta, GA, Henry Ford Health Sciences Center, Detroit, MI, Henry Ford Hospital, Detroit, MI, Mayo Foundation, Jacksonville, FL, National Institute of Neurological Disorders and Stroke, Bethesda, MD, University of California at San Diego, San Diego, CA, University of Cincinnati, Cincinnati, OH, University of Missouri, Columbia, MO, University of Texas at Houston, Houston, TX, Wayne State University, Detroit, MI

3:10 **Prospective, Monitored, Multicenter, Post-approval Experience With Intravenous t-PA for Treatment of Acute Stroke: The Standard Treatment with Activase to Reverse Stroke (STARS) Study** 77
Gregory W Albers, The STARS Investigators, Stanford Stroke Center, UCSF Stanford Health Care, Palo Alto, CA

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Phillip A. Scott, Rodney W. Smith, Carl R. Chudnofsky, Robert J. Grant, Shirley M. Frederiksen, Susan L. Hickenbottom, Willia G. Barsan, Foote Hospital, Jackson, MI, Hurley Hospital, Flint, MI, St. Joseph Merc Hospital, Ann Arbor, MI, University of Michigan, Ann Arbor, MI

Friday, February 5, 1999
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Vascular Pathology

Moderator: Gregory del Zoppa, La Jolla, CA

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Yodchai Lapakulchai, Grace Hsu, Florence Hofman, Annlia Paganini-Hill, Mark J. Fisher, USC School of Medicine, Los Angeles, CA

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Masahiko Hiroki, Shunsaku Hirai, Tokyo Metropolitan Neurological Hospital, Fuchu, Japan

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Wandong Zhang, Catherine Smith, Danica Stanimirovic, National Research Council of Canada, Ottawa, ON, Canada

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Arshad Majid, Yong Y He, Jeffrey M Gidday, Stuart S Kaplan, T S Park, Dennis W Choi, Chung Y Hsu, Washington University School of Medicine, St. Louis, MO

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Intrinsic, Hemodynamic-Independent Differences in Vulnerability to Permanent Focal Cerebral Ischemia In Common Mutant Mouse Strains

Arshad Majid, Yong Y He, Jeffrey M Gidday, Stuart S Kaplan, T.S. Park, Dennis W Choi, Chung Y Hsu, Washington University School of Medicine, St. Louis, MO

Genetically engineered mutant mice can be a potentially useful tool for studying the role of single genes in cerebral ischemia. However, since these mice are commonly derived from more than one parent strain, strain-dependent differences in vulnerability to cerebral ischemia could confound results depending on choice of wild-type controls. To test this hypothesis, permanent MCA ligation was performed via temporal craniotomy in ketamine/xylazine-anesthetized male C57Bl/6 (n=22), Balb/C (n=14), and SV129 (n=11) mice. Core body temperature was maintained at 37±0.5°C. Mice were sacrificed after 24 h and infarct volumes measured by TTC staining. There were no differences in resting or ischemic (at 30 min) blood pressure or blood gases noted among the three strains. Cortical infarcts in Balb/C mice (32.7±3.7mm^3) were at least 2.5 times larger than those found in SV129 mice (6.6±0.8mm^3) and C57Bl/6 mice (8.5±1.0mm^3); infarct size in the latter two strains were not significantly different. Ten min after MCA ligation, relative reductions in CBF in the ischemic core were similar in all three strains (n=6/strain). Analysis of the circle of Willis revealed the absence of bilateral posterior communicating arteries in 100% of C57Bl/6 and in 80% of Balb/C mice. In contrast, 80% of SV129 mice had small diameter posterior communicating arteries unilaterally or bilaterally (n=5/strain). Our findings indicate that the extent of brain injury following permanent focal ischemia by the direct ligation method varies significantly between strains. Our results suggest that intrinsic, hemodynamic-independent differences exist among these strains to account for their differential susceptibility to focal ischemia, and also underscores the importance of appropriate selection of wild-type controls.

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Persistent Monocyte Activation in Stroke Patients

Yodchai Lapakulchai, Grace Hsu, Florence Hofman, Annlia Paganini-Hill, Mark J. Fisher, USC School of Medicine, Los Angeles, CA

Recent work has emphasized important roles for both inflammation and thrombosis in stroke pathogenesis. Monocytes are known to mediate inflammation by secretion of inflammatory cytokines; monocytes can also express cell surface tissue factor, the major generator of the coagulation cascade. We studied monocyte activation in stroke patients and in control subjects matched for age and stroke risk factor status. Neopterin, secreted by activated monocytes, was significantly elevated in 67 ischemic stroke patients acutely (<4 days) (8.9±8.0 nmoles/l) (mean±SD) and during the chronic phase (two months post-stroke) (9.5±9.8 nmoles/l), compared to 83 control subjects (6.2±3.9 nmoles/l, p<.01). Tissue factor, quantitated by flow cytometry, was detectable in 8.8±9.3% and 12.3±11.8% of monocytes from acute (n=21) and chronic (n=21) stroke patients respectively, compared to 2.8±3.6% of control subjects (n=46, p<.001). Thus, monocyte activation, demonstrated by secretion (neopterin) and cell surface expression (tissue factor), is persistently increased in stroke patients. These findings suggest that monocytes play a critical dual role in stroke, as mediators of both inflammation and thrombosis.

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Tortuosities of the White Matter Medullary Arterioles Are Associated with the Severity of Hypertension

Masahiko Hiroki, Shunsaku Hirai, Tokyo Metropolitan Neurological Hospital, Fuchu, Japan

Background: Tortuosity of the white matter medullary artery is often observed in the brains of hypertensive patients, but the clinical implication has not been revealed. We performed postmortem pathological study and evaluated the relationship between the tortuosity and the severity of hypertension (HT). Methods: The brains of 38 patients (mean age: 69.3 ±10.6 years, 22 men) who died of various causes without brain edema were obtained at autopsy in our hospital. Patients who had received brain irradiation or died using respirator were excluded for the analysis. Clinical diagnosis of ischemic stroke was made in 9, hemorrhagic stroke in 1, Parkinson's disease in 11, amyotrophic lateral sclerosis in 8, other degenerative diseases in 7, Guillain-Barré syndrome in 2 patients. HT was possessed in 29 patients. The severity of HT were classified according to the classification of the World Health Organization. By light microscopic observation of the coronal sections, we measured the largest curve diameter in direction and the largest vascular diameter at the same tortuous lesion in the white matter of the corona radiata and the centrum ovale. In each patient, we represent a maximum diameter ratio of the curve to the vessel. These ratios in each HT stage were compared statistically. Results: There were no significant differences in age among the HT stages. The mean diameters of the largest vascular diameter with the maximum ratio were 51.1 ±20.1 mm in stage 0 (n=9), 41.6 ±18.6 mm in stage I (n=11), 42.5 ±25.8 mm in stage II (n=9) and 71.4 ±9.9 mm in stage III (n=9) (P<0.05 stage 0 vs stage III, P<0.005 stage I vs stage II and stage II vs stage III [ANOVA]). The mean maximum ratios were 1.58 ±0.41 in stage 0, 1.75 ±0.30 in stage I, 2.12 ±0.55 in stage II and 3.15 ±1.15 in stage III (P<0.0001 stage 0 vs stage III and stage I vs stage III, P<0.005 stage II vs stage III [ANOVA]). Conclusions: Arteriolar tortuous changes in the cerebral white matter were increased in the severe hypertensives. This may suggest a relationship to the dilated perivascular spaces which often depicted, at the corresponding region, as signal hyperintensities on T2-weighted magnetic resonance images.

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Up-regulation of ICAM-1, IL-1β, TNF-α, IL-8, and MCP-1 in Human Brain Endothelial Cells Exposed to Ischemia-Induced Mediators from Human Astrocytes or Brain Endothelium

Wandong Zhang, Catherine Smith, Danica Stanimirovic, National Research Council of Canada, Ottawa, ON, Canada

Leukocyte infiltration into brain contributes to the development of ischemic brain damage and is mediated by endothelial/leukocyte adhesion molecules, cytokines, and chemokines released by ischemic tissues. In this study, we provide evidence for both autocrine and paracrine mechanisms of human cerebromicrovascular endothelial cell (HCEC) activation in ischemia. Cultured HCEC and fetal human astrocytes (FHAS) were exposed to 4 h of either in vitro ischemia (i.e., hypoxia in an anaerobic chamber in glucose-free Krebs solution) or 100u/ml of IL-1β or TNF-α, followed by a 24 hr recovery in ambient air and fresh glucose-supplemented media. Conditioned media (CM) were collected from the ischemic or cytokine-treated FHAS and HCEC at the end of recovery period, and applied to separate HCEC cultures for 4, 8, 18, and 24 h. Semi-quantitative RT-PCR and immunocytobiochemistry demonstrated a 2~3-fold up-regulation of ICAM-1 in HCEC exposed to CMs from ischemic or cytokine-treated FHAS and HCEC. A marked elevation in mRNA levels for cytokines IL-1β and TNF-α, and chemokines IL-8 and MCP-1, was observed in HCEC exposed to either ischemic FHAS-CM or HCEC-CM. The up-regulation of both cytokine and chemokine genes in HCEC was maximal at 4-8 h after the addition of ischemic CMs. CMs from cytokine-treated HCEC or FHAS also induced a pronounced up-regulation, lasting up to 24 h, of all genes in HCEC investigated. CMs from TNF-α-treated cells were less potent than CMs from IL-1β-treated cells. CMs from cytokine-treated FHAS were more potent than HCEC-CMs in inducing IL-1β gene in HCEC. These results indicate that HCEC and FHAS are important sources of pro-inflammatory mediators in ischemia, which affect HCEC activation via both autocrine and paracrine routes.

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Laser Thrombolytic Therapy for Experimental Cerebral Thrombosis

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Objective: Current lytic therapies may increase the risk of intracranial hemorrhage due to systemic lytic effects. Intra-arterial (IA) laser thrombolysis (LT) was used to assess the ability to rapidly and safely remove occlusive clot in an acute setting without adjunctive lytic therapy. Methods: The internal carotid arteries (ICA) of 7 domestic swine (70-80lbs) were catheterized with an 8F guiding catheter. A 2mm by 4cm clot segment, aged 3-24hrs. was injected into the ICA to achieve total occlusion. The LT catheter, consisting of a delivery catheter housing an optical fiber bundle, was placed through the clot, up to the rete. A Palomar pulsed dye laser emitted 577nm light that is selectively absorbed by clot and not vessel wall. TIMI grade and % recanalization were assessed angiographically. Histology was performed on treated vessels. Results: In seven animals, a total of 8 ICA's were treated with laser thrombolysis. Six of eight treated vessels achieved a TIMI flow of ≈2 and % recanalization of ≥75% was achieved in 5 of 8 vessels. Two of the 8 ICA's had clot resistant to LT. Laser energy was 33.5 ± 3mJ and number of pulses was 910 ± 474 at 3 Hz during 5 minutes of lasing. Four control vessels remained at TIMI 0 following catheter manipulation only. There was no angiographic evidence of vessel damage. Histology revealed no adverse effects on vessels or surrounding tissue due to laser energy. Conclusions: Laser thrombolysis appears to be a safe and feasible method of removing occlusive thrombi in cerebral arteries with rapid restoration of blood flow. Further efficacy studies are in progress.

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Initial Volume of Protein Synthesis Inhibition Predicts Size of Delayed Tissue Infarction Following 1 h Transient Focal Cerebral Ischemia In Mice.

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In the surrounding of permanent focal ischemia, the area of cerebral protein synthesis (CPS) inhibition is much larger than that of energy failure. With increasing time after focal ischemia this "metabolic penumbra" turns into complete infarction due to growth of the area of energy failure but not of CPS inhibition. We examined whether this pathomechanism is also involved in the manifestation of brain infarction following the onset of transient cerebral focal ischemia. Mice were subjected to middle cerebral artery occlusion for 1 h by the intraluminal filament technique followed by no or recirculation for 1 h, 6 h, 1 d, and 3 d, respectively (n = 4/5). Fortyfive minutes prior to the end of the experiment, 3H-labeled leucine was injected i.p. for the autoradiographic measurement of regional cerebral protein synthesis (CPS). Brains were then frozen in situ with liquid nitrogen to determine ischemic injury by regional bioluminescence for ATP. The area of CPS inhibition and ATP depletion was assessed in five planes to calculate the volumes of metabolic deficits. At the end of 1 h focal cerebral ischemia, the volume of CPS inhibition amounted to 107 ± 15 mm^3 (mean ± SD) and did not change significantly during the 1 h - 3 d recirculation period (1 h: 86 ± 30 mm^3; 6 h: 108 ± 26 mm^3; 1 d: 88 ± 22 mm^3; 3 d: 83 ± 13 mm^3). At 1 h post-ischemia, the volume of ATP depletion was 65 ± 27 mm^3 thus yielding a "metabolic penumbra" of 43 ± 32 mm^3. After 1 h postischemia, ATP had recovered to the control level (1 h: 4 ± 2 mm^3; p<0.001). With longer recirculation intervals, however, the volume of ATP deficit increased to 19 ± 8 mm^3 at 6 h postischemia, to 38 ± 29 mm^3 at 1 d and to 82 ± 12 mm^3 (p < 0.05) at 3 d postischemia, reaching the volume of CPS suppression. This resulted in a significant disappearance of the "metabolic penumbra" to 1 ± 29 mm^3 (p < 0.001) at 3 d after 1 h of transient focal cerebral ischemia. Our data indicate that early postischemic CPS suppression demarcates brain tissue in which delayed tissue infarction develops. The gradual deterioration of energy metabolism probably is associated with molecular mechanisms leading to mitochondrial dysfunction.